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10/607,623	06/27/2003	Haim D. Danenberg	92114.005US1	7907
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EXAMINER JAGOE, DONNA A				
ART UNIT		PAPER NUMBER		
1614				
NOTIFICATION DATE		DELIVERY MODE		
02/09/2009		ELECTRONIC		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DOROTHY.AUTH@CWT.COM  
THOMAS.QUINONES@CWT.COM  
LINDA.RICCI@CWT.COM

### Office Action Summary

**Application No.**

10/607,623

**Applicant(s)**

DANENBERG ET AL.

**Examiner**

Donna Jagoe

**Art Unit**

1614

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 28 July 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1, 4-10, 16, 17, 19, 20, 23-26, 31-35, 39-41, 71 and 72 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 4-10, 16, 17, 19, 20, 23-26, 31-35, 39-41, 71 and 72 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 4/21/08
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

***Claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-35, 39-41, 71 and 72 are pending in this application.***

Applicants' arguments filed July 28, 2008 have been fully considered and they are deemed to be persuasive regarding previous rejections of record. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

However, upon reconsideration, the following rejections and/or objections are newly applied. They constitute the complete set presently being applied to the instant application.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-10, 16, 17, 19, 20, 23, 24, 35, 39-41, 71 and 72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1, 40 and 71 recite a "an encapsulated within a suitable carrier". The

instant specification recited that the agent must be an agent that is an intra-cellular inhibitor of specifically macrophages/monocytes and inhibits and/or destroys the macrophages and/or monocytes (paragraphs 10-13, 19, 20, 24, 25, 28 and 29).

The above disclosures, however, do not provide adequate support for an "an agent".

#### **Written Description**

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). The Examiner is guided in his opinion that Applicant has not adequately described the presently claimed subject matter by the MPEP at § 2163 - 2163.05. In particular, while Applicant's specification as originally filed contained a disclosure drawn to agents that intra-cellular inhibitor of specifically macrophages/monocytes and inhibits and/or destroys the macrophages and/or monocytes (detailed supra), such does not entitle Applicants to now claim "an agent" because such represents medicaments that were not previously set forth or that would have been immediately envisaged by one skilled in the art from the specification as originally filed. "A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996)"(emphasis added), see MPEP § 2163(I)(A). Also, "See also *In re*

*Smith*. 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) ("Whatever may be the viability of an inductive-deductive approach to arriving at a claimed subgenus, it cannot be said that such a subgenus is necessarily described by a genus encompassing it and a species upon which it reads.' (emphasis added)).", see MPEP § 2163.05(II).

Considering the teachings provided in the specification as originally filed, the Examiner finds that Applicants have failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set for the claimed invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicants had possession of the concept of "an agent" which would encompass any agent.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-10, 16, 17, 19, 20, 23, 35 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: while applicant claims the agent encapsulated within a suitable carrier from 0.03-1 micron in size, there does not appear to be an upper limit to the size as indicated by a "to". Amending the claim to

recite ...encapsulated within a suitable carrier from 0.03 to 1 micron in size... would obviate the rejection.

Claim s 4-10, 16, 17, 19, 23 and 24 recites the limitation "the method as in one of the claims 1-3" in line one of each of the claims. There is insufficient antecedent basis for this limitation in the claim because claims 2 and 3 have been cancelled.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-35, 39-41, 71 and 72 rejected under 35 U.S.C. 103(a) as being unpatentable over Pennanen et al. (U) and Hack et al. U.S. Patent No. 6,090,777 in view of Ylitalo, Gen. Pharmacology. 2002 and Hope et al. U.S. Patent No. 6,139,871 A.

Pennanen et al. teach that when bisphosphonates are encapsulated in liposomes, the inhibitory potency against proinflammatory cytokines (IL-1 $\beta$ , IL-6 and TNF- $\alpha$ ) is enhanced by a factor of 10-20. The complex formation of bisphosphonates with extracellular calcium enhanced the **uptake** of the compounds (uptake is also known as phagocytosis)(see abstract). The inhibition of inflammatory cytokine production and secretion **by macrophages** is a valuable marker for potential anti-inflammatory drugs (page 916, column 2). Liposome encapsulated clodronate was over ten times more potent inhibitor of cytokine secretion from RAW264 cells than free drug and the inhibitory potency of etidronate was also considerably increased (page 917, column 2).

It does not teach treatment of a patient having a myocardial infarction (MI). Hack et al. teach that the inflammatory reaction which occurs in the course of an acute myocardial infarction (AMI) comprises some important events: including the production of cytokines such and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin-6 and activation of complement (column 1, lines 56-63) and inhibition of this complement would reduce

or prevent myocardial damage (zone of infarct) (column 5, lines 6-18). It would have been made obvious to one of ordinary skill in art at the time it was made to administer the liposome encapsulated bisphosphonates of Pennanen et al. motivated by the teaching that the inhibitory potency against proinflammatory cytokines (IL-1 $\beta$ , IL-6 and TNF- $\alpha$ ) is enhanced by a factor of 10-20 when bisphosphonates are encapsulated in liposomes and further motivated by the teaching of Hack et al. who teach that the zone of infarct can be reduced by inhibiting the activation of complement (paragraph 5, lines 6-18), by administration of an agent that has anti-inflammatory properties and is a cytokine antagonist (claims 19 and 21) (Pennanen et al. teaches that bisphosphonates are anti-inflammatory agents that inhibit cytokine production and secretion).

Ylitalo teaches liposomal (encapsulated) formulations of bisphosphonates such as clodronate and etidronate (page 293, column 2, paragraph 3), and teach that bisphosphonates inhibit atherosclerosis (page 287, column 1 to page 288, column 2). Ylitalo teaches that bisphosphonates anti-atherogenic effect is due to a direct effect on arterial wall wherein the bisphosphonates interact with the subendothelial lipid phagocytosing cells (intracellular inhibitor)(page 292, column 1, paragraph 1) and macrophages are especially sensitive to bisphosphonates, and bisphosphonates suppress macrophages and exert cytotoxicity and suppress the appearance of macrophages in arterial wall during atherogenesis. Ylitalo does not teach depletion of macrophages, however, it teaches that the appearance of macrophages is suppressed. Since the term "depletion" is synonymous with the term "eliminating all macrophages" and both circumscribe methods of treatment having absolute success. Absolute



success is not reasonably possible with most diseases, especially ones having etiologies as complex as atherosclerosis and AMI.

Pennanen et al., Hack et al. and Ylitalo et al. do not teach the size of the liposomes.

Hope et al. teach liposomes of 0.1 to 0.15 microns for treatment of atherosclerosis (see abstract). It would have been made obvious to one of ordinary skill in art at the time it was made to treat AMI in a patient by administering encapsulated bisphosphonates in liposomes in a size of 0.1 to 1 micron motivated by the teaching of Pennanen et al. who teach that liposomal bisphosphonates are 10-20 times more potent in inhibiting proinflammatory cytokines and the teaching of Hack et al. who teach that by inhibiting proinflammatory cytokines, formation of complement is inhibited and thus the zone of infarction is reduced. Regarding the size of the liposome, instant claims 1, 25 and 71 is drawn to a formulation with a size range of 0.03-1 micron. Hope et al. teach a liposome formulation in a range of from 0.1 to 0.15 microns. This amount overlaps and encompasses the claimed size. A *prima facie* case of obviousness exists where the claimed ranges are close enough that one skilled in the art would have expected them to have the same properties.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

***Response to Arguments***

Applicant's arguments with respect to claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-35, 39-41, 71 and 72 have been considered but are moot in view of the new ground(s) of rejection.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-

0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe /D. J./  
Examiner  
Art Unit 1614

January 27, 2009

/Ardin Marschel/  
Supervisory Patent Examiner, Art Unit 1614

